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ACTA PHYSIOLOGICA SCANDINAVICA
VOL. 54. SUPPLEMENTUM 186

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DIFFERENTIAL SUPRASPINAL CONTROL OF SYNAPTIC ACTIONS EVOKED BY VOLLEYS IN THE FLEXION REFLEX AFFERENTS IN ALPHA MOTONEURONES

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CARL BLOMS BOKTRYCKERI A.-B.

Contents

Introduction 5

Remarks on the synaptic actions exerted by the FRA and the supraspinal control of reflex arcs 6

Methods 8

Chapter I. Effects of brain stem lesions on actions by conditioning volleys in somatic afferents 10

A. Conditioning volleys in muscle afferents 10

B. Conditioning volleys in high threshold joint and skin afferents 19

Summary 21

Chapter II. Effects of brain stem lesions on actions evoked by natural stimulation of receptors 22

A. Muscle receptors 22

B. Skin receptors 25

Summary 27

Chapter III. Analysis of the inhibitory path from the FRA to flexor motoneurones 29

A. Intracellular recording from flexor motoneurones after a low pontine lesion 29

B. Exclusion of Wilson's disinhibition 31

C. The relationship between the excitatory and the inhibitory path from the FRA to flexor motoneurones 34

Summary 35

Chapter IV. Reflex actions in anaesthetized animals with intact brain 37

Summary 39

Discussion 40

General summary 46

References 48

Introduction

In the recent era of research on spinal cord organization the main emphasis has been on the connexions of the large muscle afferents, whereas the flexion reflex actions have not received so much attention. It should be remembered, however, that SHERRINGTON's investigations on the flexion reflex remain the basis for important principles in spinal cord organization. The concept of reciprocal innervation arose from the findings on the flexion reflex actions and was formulated by SHERRINGTON (1906): 'the reflex inhibition (relaxation) and the reflex excitation (contraction) are part and parcel of one and the same reflex reaction; and that although opposite in direction they are coordinate reciprocal factors in one united response'. In further investigations SHERRINGTON (1910) classified muscles as flexors or extensors partly depending on whether they contracted or relaxed during the flexor reflex, evoked by a standard test stimulus.

In electrophysiological experiments it has been shown that excitatory action is evoked in flexor and reciprocally inhibitory action in extensor alpha motoneurones by impulses in group II and III muscle afferents (LLOYD 1943, 1946, BROCK, ECCLES and RALL 1951, LAPORTE and LLOYD 1952, LAPORTE and BESSOU 1959, ECCLES and LUNDBERG 1959 a, b, PAINTAL 1961), in cutaneous afferents (LLOYD 1943, HAGBARTH 1952, LAPORTE and BESSOU 1958, ECCLES and LUNDBERG 1959 a, b), and in high threshold joint afferents (ECCLES and LUNDBERG 1959 a, b). These afferents have been denoted the *flexion reflex afferents* (*FRA*) (ECCLES and LUNDBERG 1959 a, HOLMQVIST, LUNDBERG and OSCARSSON 1960).

In order to appreciate the functional significance of the flexion reflex actions it has proved necessary to take into account the supraspinal control of their reflex arcs. In the decerebrate cat the synaptic actions of the FRA are small or absent (JOB 1953, ECCLES and LUNDBERG 1959 b, HOLMQVIST and LUNDBERG 1959 a, b, KUNO and PERL 1960) because of a tonic inhibitory control from supraspinal centres of the interneurones mediating the actions from the flexion reflex afferents. A similar control has been found of the I b pathways but not of the I a inhibitory pathway (ECCLES and LUNDBERG 1959 b). Some aspects of the organization of this

inhibitory controlling system in the cat has been revealed (HOLMQVIST and LUNDBERG 1959 a). The descending pathway is located in the dorsal part of the lateral funicles and from each side a bilateral effect is exerted. The centres maintaining the inhibition of the interneurones of these reflex arcs can operate independently of those responsible for decerebrate rigidity, as is also shown by the fact that decerebrate rigidity depends on ventral pathways (FULTON, LIDDELL and RIOCH 1930, DOWNMAN and HUSSAIN 1958). The control of spinal interneurones mediating the actions of the flexion reflex is exerted from medially located brain stem centres, it remains after a bilateral removal of the vestibular nuclei but disappears after a medial lesion at obex (DOWNMAN and HUSSAIN 1958, HOLMQVIST and LUNDBERG 1959 a).

For the further analysis we wanted to learn at which level the responsible centres were located and transverse lesions were made at progressively more caudal levels in the medial brain stem. The effects of these lesions will be described in this paper. It has turned out that the control mechanism is complex and indicating new interesting principles for the organization of spinal reflexes. There is evidence of independent control of the reciprocal actions to extensor and flexor motoneurones, and equally important is the finding that after a low pontine lesion impulses in the FRA evoke inhibition in flexor motoneurones (*cf.* ECCLES and LUNDBERG 1959 a). A preliminary report of some of the findings has been published (HOLMQVIST and LUNDBERG 1959 b).

Remarks on the synaptic actions exerted by the FRA and the supraspinal control of reflex arcs

When using the technique of conditioning monosynaptic reflexes it is important to realize that there are different mechanisms whereby a conditioning volley may change the size of a monosynaptic test reflex. A conditioning volley may evoke excitatory or inhibitory synaptic actions in motoneurones (BROCK, COOMBS and ECCLES 1952, COOMBS, ECCLES and FATT 1955 a, b), thereby changing the excitability of the motoneurones and the size of the monosynaptic reflexes. On the other hand a conditioning volley may depress a monosynaptic test reflex on the presynaptic side (FRANK and FUORTES 1957, FRANK 1959, ECCLES, ECCLES and MAGNI 1960, ECCLES 1961). In this case the reflex is depressed even when the conditioning volley does not exert any recordable synaptic action in the motoneurones, presumably because the conditioning volley depolarizes the presynaptic fibres in the testing reflex arc (ECCLES *et al.*, 1960).

The investigations by ECCLES and LUNDBERG (1959 b) and HOLMQVIST and LUNDBERG (1959 b) on the supraspinal control of reflex arcs have been concerned with the former actions and not with presynaptic inhibition as has been proved in parallel investigations with intracellular recording of post-synaptic potentials.

When relying exclusively on the technique of conditioning monosynaptic reflexes for disclosure of excitability changes in motoneurones great caution must be taken when investigating group I synaptic actions from flexor muscles because they provide presynaptic inhibition of the monosynaptic Ia pathway (FRANK and FUORTES 1957, ECCLES *et al.*, 1960). On the other hand ECCLES *et al.* (1960) found no or little evidence for presynaptic inhibition of the monosynaptic Ia pathway from high threshold muscle afferents and the technique of conditioning monosynaptic reflexes should be satisfactory for revealing excitability changes evoked in motoneurones from these afferents.

In connexion with the existence of presynaptic inhibition it is of interest that KUNO and PERL (1960) have claimed that in the decerebrate state, volleys in group II and III afferents from BSt inhibit test reflexes from gastrocnemius-soleus. In our experience group II and III effects from the BSt nerve are equally well suppressed in the decerebrate state as the corresponding effects from other nerves. In similar experiments on decerebrate cats R. M. ECCLES and LUNDBERG (unpublished) sometimes found inhibition of gastrocnemius-soleus and flexor digitorum longus test reflexes from posterior biceps-semitendinosus, but evoked exclusively by group I volleys. It was confirmed by intracellular recording that this inhibition was presynaptic, *i.e.* group I volleys from BSt did not evoke any synaptic action in gastrocnemius-soleus motoneurones, whereas the homonymous monosynaptic EPSP was decreased. The inhibitory effect from BSt described by KUNO and PERL (1960) has the latency and initial time-course of presynaptic inhibition. We do assume that it is a group I effect and that they have failed to differentiate between effects evoked by low and high threshold muscle afferents.

The mechanism by which supraspinal centres exert control of spinal reflex arcs also deserves comment. Since in the decerebrate state volleys in certain afferents failed to evoke synaptic actions in motoneurones it was postulated that interneurones of their pathways were inhibited from the brain stem (ECCLES and LUNDBERG 1959 b). Support for this postulate is provided by the observation that activation of the inhibitory supraspinal control system evokes large inhibitory potentials in interneurones (in and around the intermediate nucleus), which can be excited by volleys in somatic afferents (LUNDBERG and VOORHOEVE 1961 b). On stimulation of the sensory-motor cortex, on the other hand, excitatory post-synaptic potentials (EPSPs) are evoked in these interneurones and correspondingly many spinal reflex arcs are facilitated by pyramidal activation (LUNDBERG and VOORHOEVE 1961 a).

Methods

The experiments were, when not otherwise stated, made on unanaesthetized decerebrate decerebellectomized cats. Ether was used during the operation and was administered in suitable mixture with air and oxygen to give a constant depth of anaesthesia. Recording was started 2 hours after withdrawal of ether. During the experiment the animals were immobilized with Flaxedil and artificially respirated. The blood pressure was continuously measured in most of the experiments and intravenous infusion of Dextran given if there were signs of circulatory failure.

In most of the experiments the synaptic actions were investigated by conditioning monosynaptic test reflexes from posterior biceps-semitendinosus, gastrocnemius-soleus and tibialis anterior+extensor digitorum longus (deep peroneal). To evoke monosynaptic reflexes double stimuli were often given, the strength of the first stimulus was subliminal for discharge of the motoneurones but facilitated the second volley (ECCLES and LUNDBERG 1959 b). The advantage of this technique is that relatively large monosynaptic reflexes can be obtained and the size of the reflex can easily be adjusted. After pontine lesions the excitability of the alpha motoneurones increases considerably and to equal the size of monosynaptic reflex evoked by double volleys in the decerebrate cerebellectomized state it was after a low pontine lesion often sufficient to use single submaximal Ia stimulation. In most of the experiments the monosynaptic reflexes were recorded from the ventral roots but sometimes recording was made from the peripheral muscle nerve. If so the ventral roots were intact and the reflex evoked by a single volley in the appropriate dorsal root.

For conditioning single stimuli were given to various muscle and cutaneous nerves and to the posterior knee joint nerve. Condenser discharges (half time of decay 45 μ sec) were used for stimulation. Even at maximal strength these pulses did not activate C-fibres. 4—6 different conditioning strengths were generally used for each muscle nerve and the strength always measured relative to threshold strength for the nerve (*cf.* ECCLES and LUNDBERG 1959 b). At each strength usually 10—15 different intervals between conditioning and testing volley were selected and 10—20 superimposed records were taken (*cf.* Fig.1).

In some experiments a simplified technique was applied to measure the effect of a conditioning volley by superimposing about 200 monosynaptic test reflex in one photographic exposure (*cf.* Fig. 7). In order to obtain a scatter of the traces on the records the test reflex was automatically delayed in successive sweeps so as to traverse the screen, and for each record this procedure was repeated 4—5 times. The CRO brightness of the baseline was kept very weak and brightening pulses were applied to the grid of the CRO during the discharges. The super-

imposed unconditioned test reflexes give a band of a certain width and the effect of a conditioning volley given at a fixed interval after the sweep start is displayed as a widening (facilitation) or narrowing (inhibition) of the band.

Intracellular recording from motoneurones was made as described by BROCK *et al.* (1952) with microelectrodes filled with 3 M KCl or 0.6 M K_2SO_4.

Brain stem lesions were made with a 3 mm wide spatula perpendicularly from the floor of the 4th ventricle and always through the entire medial brain stem. After the experiment the brain stem was fixed in 10 per cent formalin. Lesions in the spinal cord were controlled histologically as described by LAPORTE, LUNDBERG and OSCARSSON (1956 a).

Chapter I

Effects of brain stem lesions on actions by conditioning volleys in somatic afferents

The effect of conditioning volleys in muscle, joint and cutaneous afferents has been tested on monosynaptic reflexes from extensors and flexors after lesions at various brain stem levels.

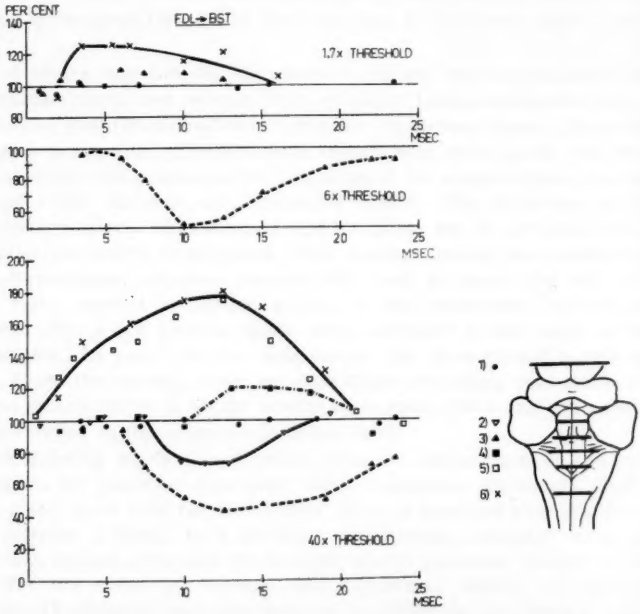

Fig. 1. The effect of a conditioning volley in the nerve to flexor digitorum longus (FDL) on the monosynaptic test reflex from the nerves to posterior biceps-semitendinosus (BSt). 100 % on the ordinate represents the unconditioned amplitude of the test reflex. Conditioned amplitude, expressed as percentage of control amplitude, is plotted as a function of time interval between the incoming conditioning and testing group I volleys recorded in the dorsal root entry zone. The measurements were obtained after the lesions indicated in the drawing. The conditioning strengths, expressed in multiples of threshold strength are indicated in each set of curves. Unanaesthetized cat.

A. Conditioning volleys in muscles afferents

Fig. 1 and 2 are from the same experiment and the curves show the effects of single conditioning volleys from the nerve to flexor digitorum longus (FDL) on monosynaptic test reflexes from the posterior biceps-semitendinosus (BSt) (Fig. 1) and the medial gastrocnemius (med.G) (Fig. 2) nerves. The curves were obtained after the lesions indicated in the schematic drawing in Fig. 1. In the decerebrate state, lesion 1 (●), there was no effect by a conditioning volley evoked either at 1.7 times threshold, which was maximal for group I, or at 40 times threshold. After lesion 2 (▽) there was, at a conditioning strength of 40 times threshold, release of inhibition to motor nuclei of extensors as well as flexors and after lesion 3 (▲) these inhibitory effects increased considerably. There were no marked effects by group I volleys after this lesion, but the conditioning FDL volley, evoked at 6 times threshold, caused inhibition of the Bst test reflex to 50 % and of the med.G test reflex to 20 % (Fig. 1 and 2). With lesion 4 (■) there was no significant change of the inhibition to the extensor nucleus (middle curve Fig. 2) but in the flexor nucleus inhibition reversed to a small facilitation. With lesion 5 (□) this facilitatory action increased and did not change with section 6 (×) below obex. Inhibitory curves to the extensor nucleus were not taken after lesion 5 but after lesion 6 the inhibitory effect evoked at 6 and at 40 times threshold

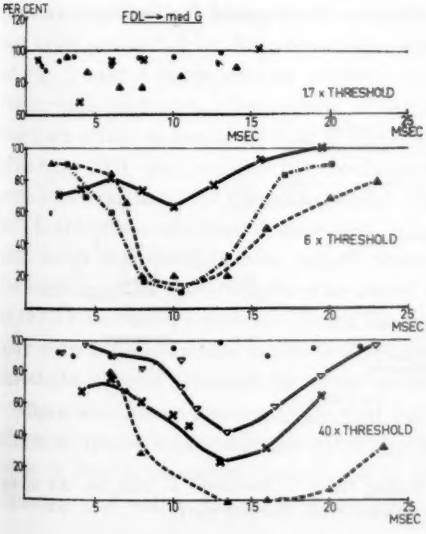

Fig. 2. The curves were obtained in the same experiment as those of Fig. 1 but the monosynaptic test reflex was evoked from the nerve to medial gastrocnemius (med. G.).

was smaller than after lesion 3 and 4. Such a decrease was usually not observed (*cf.* Fig. 4) and was possibly due to a deterioration in the preparation such as may easily occur after transection of the cord. Our impression is that the pontine lesion at which there is maximal inhibitory action to flexor motor nuclei there is concomitantly maximal or nearly maximal release of the inhibitory path from high threshold muscle afferents to extensor motor nuclei. In the experiments of Fig. 1—4 the lesions were restricted to the medial part of the brain stem but no difference was found when the lesion was extended laterally so that the whole brain stem was transected.

The interneurones mediating group I b actions are also tonically inhibited from centres in the brain stem in the decerebrate cat (ECCLES and LUNDBERG 1959 b) and the release of this control was also investigated after various lesions in the brain stem. The effects in the upper curves of Fig. 1 and 2 are difficult to judge but the findings in Fig. 4 are representative for experiments in which there was a clear I b inhibitory action in the spinal state. The upper plot in Fig. 4 shows that there was no significant release of the group I path from FDL to gastrocnemius-soleus (G-S) after lesion 3 (▲), which caused an opening of the inhibitory path from high threshold muscle afferents to flexor motoneurones (Fig. 3, lower curve ▲) and concomitantly an almost maximal release of the inhibitory path to extensors from these afferents (Fig. 4, lower curve ▲). Apparently medullary centres suffice to maintain the tonic inhibitory control of interneurones of the I b inhibitory path, whereas pontine centres are required for the tonic control

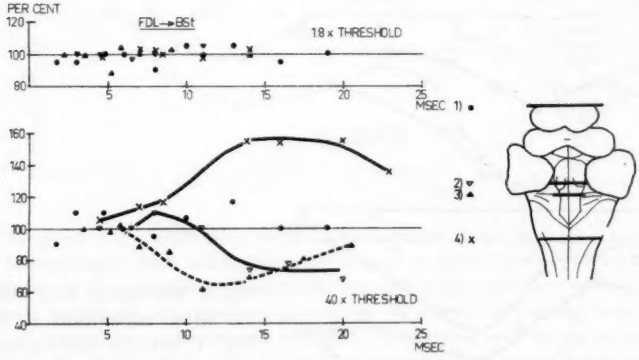

Fig. 3. As in Fig. 1 showing the conditioning effect in the nerve to FDL on the monosynaptic test reflex evoked from the BSt nerve.

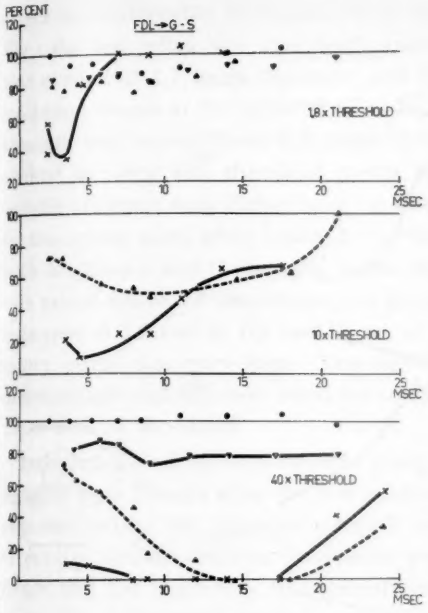

Fig. 4. These curves were obtained in the same experiment as those of Fig. 3 and show the effect on monosynaptic test reflexes evoked from the gastrocnemius-soleus (G-S) nerve.

of the inhibitory path to extensor nuclei from high threshold muscle afferents. Evidence for a differential supraspinal control of the I b inhibitory path and of the inhibitory path from the FRA to extensor motoneurones has been presented by ECCLES and LUNDBERG (1959 b). In the experiment of Fig. 3 and 4 there was no evidence of a group I b excitatory action to flexor motoneurones after section of the spinal cord (upper curve, Fig. 3). Such an effect is found in Fig. 5 where in the spinal state the facilitatory effect on BSt was evoked by conditioning the G-S nerve at a maximal group I strength of 1.7 times threshold. This effect was caused by impulses in I b afferents, because it appeared at a strength of 1.3 times threshold and when the strength was raised above 1.7 there was no increment in facilitation until the strength was raised to 2.0 times threshold. A release of the I b excitatory pathway from the tonic inhibitory control was found only with lesions caudal to the one opening the inhibitory path from high threshold muscle afferents to flexor motoneurones.

There was never any evidence that I b impulses could evoke inhibitory action in flexor motoneurones after the low pontine lesion. In the experiment of Fig. 5 recording was made in the S 1 ventral root and the conditioning G-S volley gave a monosynaptic discharge as large as the testing

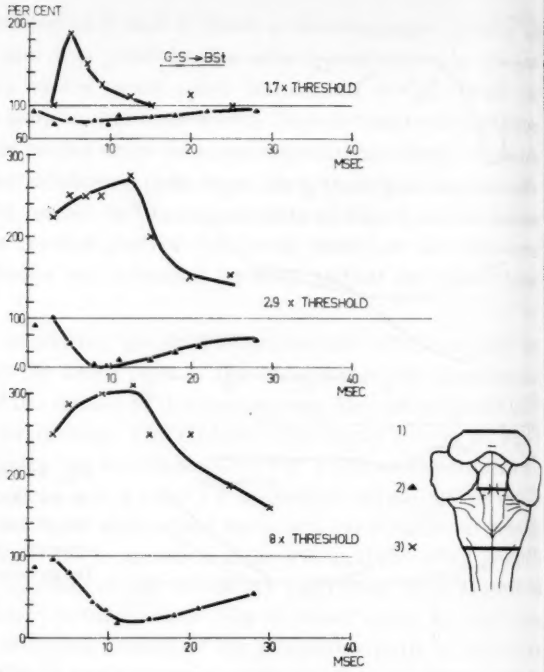

Fig. 5. As in Fig. 1 but the conditioning volley was in the nerve from gastrocnemius-soleus (G-S).

one from BSt. The small inhibitory action by the group I volley from G-S in the upper curve (Fig. 5) was probably neither a I b effect nor an effect due to stimulation of low threshold group II fibres, but presumably a Renshaw effect secondary to the monosynaptic discharge from G-S. This can be stated because the inhibitory effect appeared at a stimulus strength only slightly above threshold for the monosynaptic reflex from the G-S nerve. It became maximal at a stimulus strength of 1.3 times threshold, at which strength G-S monosynaptic reflex was maximal, and it did not increase when the stimulus strength was raised to activate fibres of the high threshold group I range (*cf.* ECCLES, ECCLES and LUNDBERG 1957 a).

The curves of Fig. 5 are of particular interest because of the large effects caused by impulses in low threshold group II fibres, which in the nerve from gastrocnemius-soleus have been identified as spindle afferents with flower spray endings (HUNT 1954). In the decerebrate state (no curves shown in Fig. 5) conditioning at a strength of 40 times threshold had no effect. After the low pontine lesion (▲) there is inhibition to 40 % at a conditioning strength of 2.9 times threshold and at 8 times threshold the

effect is considerably increased. At 16 times threshold (not shown in the Fig.) the test reflex was completely inhibited. A maximal group I volley was evoked at 1.7 times threshold and there was no increment from the inhibition shown in the upper curve in Fig. 5 until the conditioning stimulus strength was raised above 2.0 times threshold. Hence inhibition may be evoked by very low threshold group II afferents and we assume that spindle afferents with flower spray endings are responsible for this effect. In the spinal state after lesion 3 (×) there was a release of facilitation both at group I and II strength. When the conditioning stimulus strength was raised above 1.7 (maximum for group I) an increment in facilitation appeared at 2.0 and in the middle curve at 2.9 times threshold the facilitatory effect was very large. The facilitation increased somewhat both in magnitude and duration when the conditioning strength was raised from 2.9 to 8 times threshold.

In a number of the experiments group II volleys had no effect on test reflexes from flexors after the low pontine lesion, but an inhibitory effect appeared when the stimulus strength was raised to activate group III afferents. Similar findings have been made with the excitatory path to flexor and the inhibitory to extensor motoneurones after partial release from the supraspinal control and presumably indicate low transmittability in these reflex paths. Lack of group II effects is sometimes also observed in the spinal state (ECCLES and LUNDBERG 1959 a).

After a low pontine lesion volleys in high threshold muscle afferents were found to inhibit monosynaptic reflexes from all flexors investigated. This is illustrated for gracilis (Grac) in Fig. 6 and 12, for deep peroneal (DP) in Fig. 7, and for iliopsoas (Ip) in Fig. 8. Also the effects on test reflexes from posterior biceps, semitendinosus, extensor digitorum longus and tibialis anterior were separately investigated; all of them were inhibited by volleys in high threshold muscle afferents from extensors in the low potine preparation. This inhibition could be evoked from all extensors investigated, quadriceps (Q), FDL, G-S, and plantaris (Pl). The inhibitory effects were often more marked to DP than to the other flexors. In the low potine preparation high threshold volleys from nerves to flexor muscles are also effective inhibitors to monosynaptic reflexes from flexors as illustrated in Fig. 6 in which the test reflex from Grac was conditioned by volleys from the DP nerve. To the left are shown the effects after the low pontine lesion, the conditioning strength being 1.4 (just maximal for group I), 3.2, 9.0 and 45 times threshold. After transection of the cord (curves to the right) there was the usual reversal to

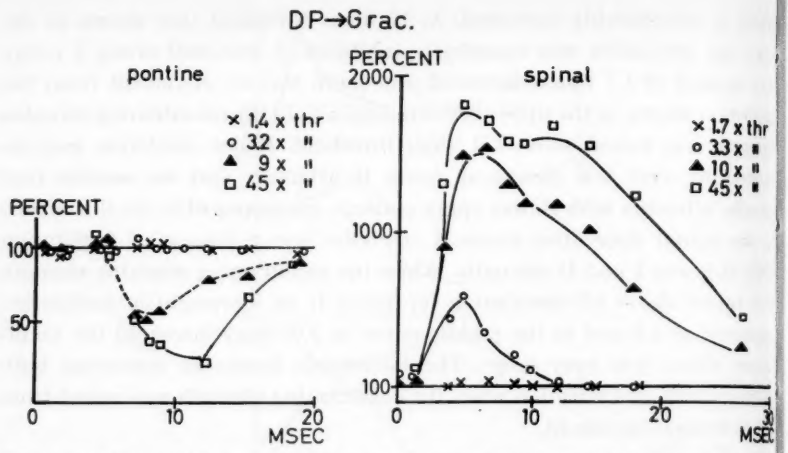

Fig. 6. As in Fig. 1 but the conditioning volley was in the nerves to extensor digitorum longus and tibialis anterior (DP) and the monosynaptic test reflex was evoked from the nerves to gracilis (Grac) and semitendinosus. The left curves were obtained after a low pontine lesion and the right curves after spinal transection in L_1. The curves were obtained at different strengths of conditioning stimulation and given in multiples of threshold strength.

facilitation. Inhibition in the low pontine preparation was found with all combinations of conditioning and testing between BSt, DP and Grac.

The low pontine lesion not only releases some inhibitory reflex arcs but also increases the excitability of alpha motoneurones. In the experiment of Fig. 7 the DP test reflex was conditioned from FDL at just maximal group I strength (middle row) and at 58 times threshold (lower row). The records in each column were taken after the lesions indicated in the headings. The height of the DP test reflex was adjusted after the various lesions but the changes in the alpha excitability is reflected by the size of the monosynaptic reflex discharge evoked by the conditioning volley (solid black spike in the two lower rows of records). After a low pontine lesion the monosynaptic reflex from FDL increases enormously (E and F). Records G—I were taken after section of the ventral quadrants in Th 10. The inhibitory action from high threshold afferents is maintained after this lesion (*cf.* HOLMQVIST and LUNDBERG 1959 a) but the monosynaptic reflex from FDL has decreased to about the same size as in B and C. This shows that the high alpha excitability in the low pontine state depends on ventral pathways. Release to a spinal state after section of the remaining dorsal quadrants is shown in K—L. It was a regular finding that the

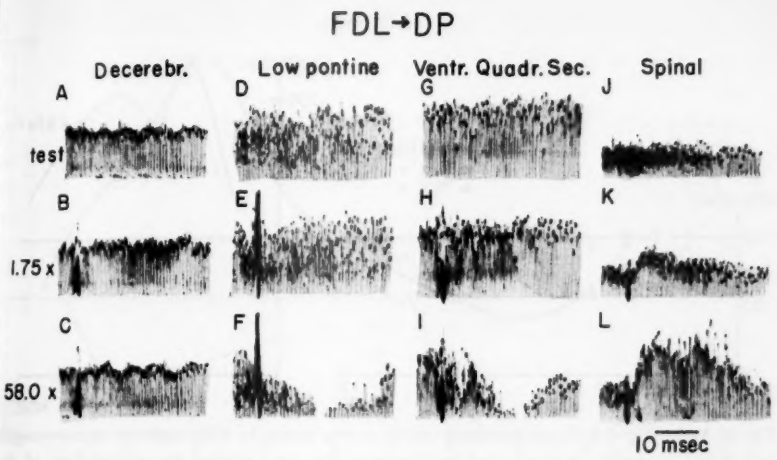

Fig. 7. The records consist of superimposed traces of many monosynaptic reflex discharges evoked from the nerve to DP and recorded in the L_7 ventral root. The records were obtained in the decerebrate state (A—C), after a low pontine lesion (D—F), after transection of the ventral quadrants in Th_{10} (G—I), and after complete spinal transection (J—L). The unconditioned test discharges are shown in A, D, G and J. The effect of a conditioning volley in the nerve to FDL is shown in the two lower rows of records and the stimulus strengths expressed in multiples of threshold strength for the nerve are indicated to the left of each row. The strength of 1.75 times threshold was just maximal for group I. The solid black spike in the beginning of records B, C, E, F, H, I, K and L is the monosynaptic discharge in L_7 evoked by the conditioning volley in FDL. All records were taken at the same amplification. Some of the records are retouched.

monosynaptic reflexes increased after the low pontine lesion and this happened not only with reflexes from extensors but to a similar extent with the monosynaptic reflexes from nerves to flexors. The pronounced alpha rigidity (*cf.* GRANIT 1955, TERZUOLO and TERZIAN 1953) obtained by anaemic decerebration (POLLOCK and DAVIS 1923, 1927, 1930), whereby half the cerebellum and a considerable part of pons is destroyed, is probably due mainly to destruction of pontine structures.

It is known that I a fibres from certain flexors, particularly BSt, make monosynaptic connexions with extensors (anterior biceps and semimembranosus) (ECCLES and LUNDBERG 1958). It is therefore possible that a testing volley from such a flexor may excite extensor as well as flexor motoneurones to discharge into the recording ventral root. This is especially likely after a low pontine lesion, which enhances the excitability of alpha motoneurones (Fig. 7). Thus when, after a low pontine lesion,

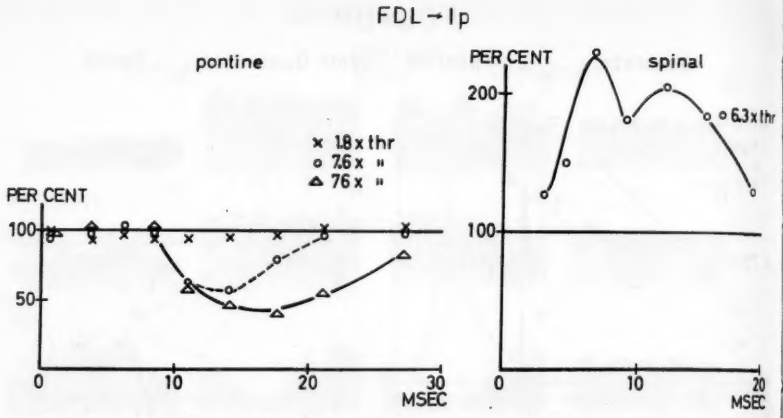

Fig. 8. As in Fig. 1 but conditioning volley in the nerve to FDL and the monosynaptic test reflex recorded in the nerve to iliopsoas (Ip) and evoked on stimulation of the dorsal 5th lumbar root. In this experiment the 4th, 5th and 6th lumbar dorsal roots were cut close to the dorsal root ganglion but the ventral roots of these segments were intact. In the 7th lumbar and 1st sacral segments the dorsal roots were intact but the ventral roots cut. The left curves were obtained after a low pontine lesion and the right curve after a spinal transection in Th_{12}. The conditioning stimulus strengths are given in multiples of threshold strength. A just maximal group I volley from FDL was evoked at a strength of 1.8 times threshold.

the monosynaptic ventral root discharge is reduced by a conditioning volley in high threshold muscle afferents, this reduction could be due to the inhibitory removal of some fraction of the ventral root spike contributed by extensor motoneurones alone.

To show that flexor motoneurones were in fact inhibited, monosynaptic reflexes were recorded peripherally in the nerves to Ip, Grac, semitendinosus (St) and DP. With the former two nerves monosynaptic reflexes were evoked by single stimuli to the sectioned L 5 and L 6 dorsal roots; in both cases these test reflexes could be inhibited by volleys in high threshold muscle afferents as is illustrated for Ip in Fig. 8. When testing St or DP the ventral and dorsal roots were intact and the stimulating and recording electrodes were on the muscle nerve; the test stimulus was limited to a part of the I a volley and was subthreshold for the alpha efferents. Conditioning volleys from other muscle nerves inhibited these test reflexes effectively in the low pontine state and when the stimulus strength was raised above 5 times threshold there was a large increment in inhibition that could not have been caused by Renshaw inhibition from antidromic impulses in alpha afferents, but must be ascribed to impulses in high threshold afferents.

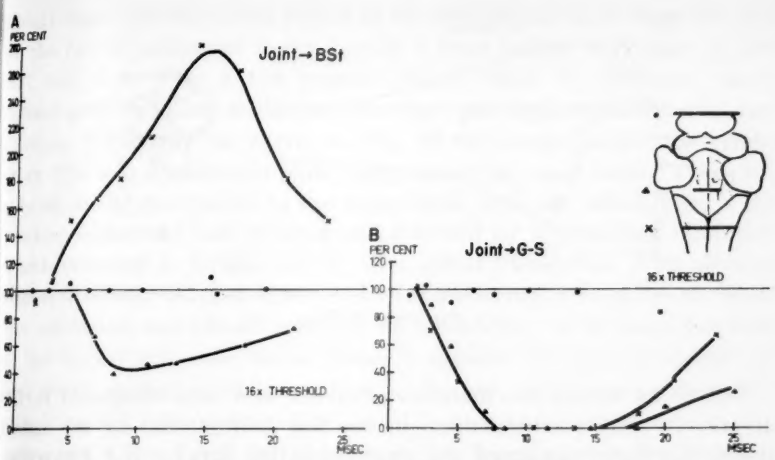

Fig. 9. As in Fig. 1 but conditioning volley in the posterior nerve from the knee joint (Joint). The effect on monosynaptic test reflexes from BSt are shown in A and on test reflexes from gastrocnemius-soleus (G) are shown in B.

B. Conditioning volleys in high threshold joint afferents and in skin afferents

High threshold joint afferents and skin afferents act synergically with high threshold muscle afferents in a varity of neuronal systems (OSCARSSON 1957, 1958, ECCLES and LUNDBERG 1959 a, HOLMQVIST et al., 1960) and it will now be shown that after a low pontine lesion volleys in these afferents evoke similar effects as a volley in high threshold muscle afferents. The curves in Fig. 9 A show the effects of a volley from the posterior nerve to the knee joint on the BSt monosynaptic reflex. In the decerebrate state this conditioning volley had no effect (●) but after a low pontine lesion, which also released inhibitory action from high threshold muscle afferents, the same volley gave rise to a marked inhibition (▲). After a section below obex (×) there was a reversal to facilitation, the characteristic effect in the spinal preparation. The inhibitory action in the low pontine state, like the excitatory in the spinal (*cf.* ECCLES and LUNDBERG 1959 a), only appeared when the stimulus strength was raised above 2—3 times threshold; presumably it is caused by fibres in the prominent group of 7—2 μ (SKOGLUND 1956). The curves in Fig. 9 B show that in the decerebrate state there was no action from the joint nerve on an extensor test reflex (●), but that a release occurred after a low pontine lesion (▲); after spinal section the inhibition decreased somewhat in duration (×).

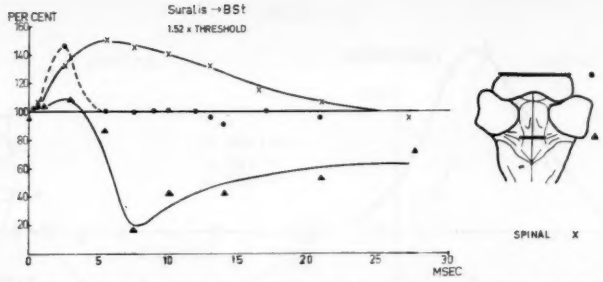

Fig. 10. As in Fig. 1 but conditioning volley in the sural nerve. The spinal transection was made in Th_{12}.

Actions by volleys in cutaneous afferents were also compared in the decerebrate decerebellectomized, in the low pontine and in the spinal states. We have confirmed the observation by ECCLES and LUNDBERG (1959 b) that in the decerebrate state the cutaneous effects are less regularly as completely suppressed as those from high threshold muscle afferents. There are sometimes in the decerebrate state marked facilitatory actions to flexor and inhibitory to extensor test reflex. In other experi-

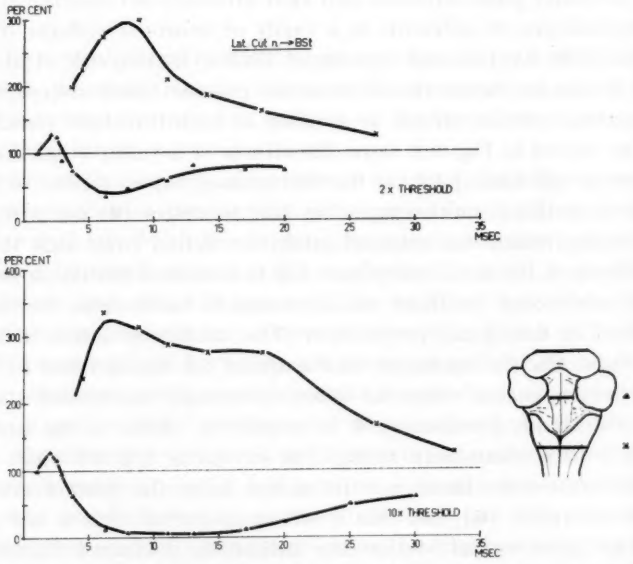

Fig. 11. As in Fig. 1 but conditioning volley in the lateral cutaneous nerve.

ments there are only small effects in the decerebrate state; from the sural or the lateral cutaneous nerve, usually a short lasting facilitation to both BSt and G-S. After a low pontine lesion volleys in cutaneous nerves caused predominantly inhibition, but there was regularly some initial facilitation. To obtain the curves in Fig. 10 the monosynaptic test refelex from BSt was conditioned with volleys from the sural nerve. There was a brief initial facilitation in the decerebrate state (●) which after a low pontine lesion (▲) was reduced and followed by a prevailing inhibition, which reversed to facilitation (×) after spinal transection. With stronger stimulation very marked effects were sometimes found as in Fig. 11 where the inhibition was almost complete on stimulation at 10 times threshold of the lateral cutaneous nerve. Hence it appears that also cutaneous volleys evoke marked inhibitory effects in the low pontine preparation. The effects on test reflexes from G-S and FDL were tested in the same experiments and it was found that the low pontine lesion releases the inhibitory path from cutaneous afferents to extensor motoneurones in the same way as has already been illustrated for the effects from high threshold muscle afferents and high threshold joint afferents.

Summary

The release of actions to alpha motoneurones by volleys in the FRA (group II and III muscle afferents, high threshold joint and skin afferents) and in I b afferents has been investigated after various brain stem lesions in unanaesthtized decerebrate cats.

A low pontine lesion released inhibition from the FRA to extensors as well as flexors. The inhibitory actions were found in all flexor nuclei tested (iliopsoas, gracilis, semitendinosus, posterior biceps, extensor digitorum longus and tibialis anterior).

Release of excitatory action from the FRA to flexor nuclei was found only after a more caudal lesion in the medulla.

The inhibitory and excitatory actions to flexors were evoked from the same afferent nerves.

Release of excitatory and inhibitory actions by I b volleys from extensors did not occur after a low pontine lesion but only after a more caudal medullary lesion.

The low pontine lesion produced a marked increase of the excitability in alpha motoneurones of extensors and flexors. This increased excitability depends on pathways descending in the ventral quadrants.

Chapter II

Effects of brain stem lesions on actions evoked by natural stimulation of receptors

To test the functional significance of the inhibitory actions on flexor nuclei described in chapter I, experiments with natural stimulation of muscle and skin have been made after a low pontine lesion. A comparison of these effects has been made with the actions evoked in the decerebrate and spinal states.

A. Muscle receptors

PAINTAL (1960) and BESSOU and LAPORTE (1960, 1961) have shown that most of the group III afferents are activated by pressure on the muscle. PAINTAL (1961) has found that this type of stimulation gives the same effect in motoneurones as a group III volley evoked by electrical stimulation of the nerve. Since the inhibitory pathway to flexor motoneurones is effectively activated by group III volleys, pressure of muscle has been tried in the low pontine preparation not only to study the functional significance of the inhibitory pathway from the FRA to flexor motoneurones but also to investigate whether it could be activated by the natural stimuli, which give excitation in the spinal state. In these experiments it was important to exclude that an effect of muscle pressure could be due to impulses in group I a afferents, which almost unavoidably are co-activated. Pressure was applied to the gastrocnemius-soleus-plantaris muscles, hence DP could not be used for testing because of the reciprocal I a inhibition. Neither was it possible to use BSt since its motor nucleus has the same segmental distribution as those of the above muscles and an inhibitory effect could have been caused by Renshaw inhibition secondary to monosynaptic I a activation of ankle extensor motoneurones. To avoid these complications monosynaptic reflexes from the nerve to Ip (segments L 4—L 5) or Grac (segments L 5—L 6) were used for testing. When the gracilis nerve was used, recording was made either from the fifth lumbar or from the rostral half of the 6th lumbar ventral root. The motor nuclei to gastrocnemius-soleus-plantaris are in L 7 and S 1 and

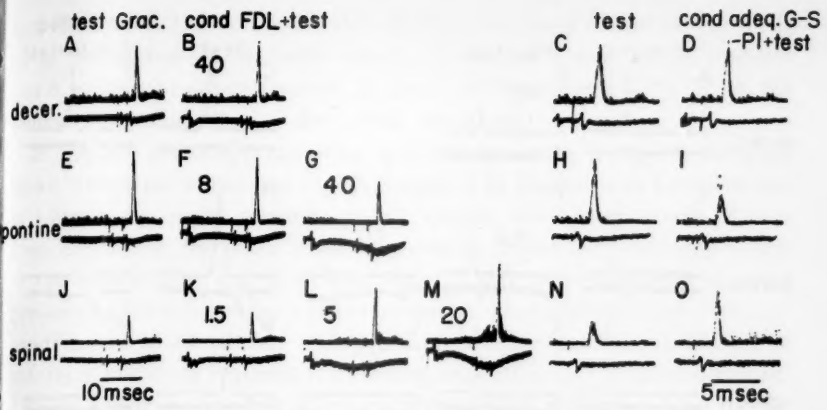

Fig. 12. The effects of a conditioning volley in the nerve to FDL (B, F, G, K, L, M) and of natural stimulation of the gastrocnemius-soleus-plantaris muscles (D, I and O) on the monosynaptic test reflex from the nerves to gracilis and semitendinosus (shown unconditioned in the upper traces in each record in A, E, J and C, H, N). The L_6 ventral root was split in two approximately equal parts and recording was made from the rostral filament. Lower traces in each record are triphasic recordings of the incoming volley from the dorsal root entry zone. In records D, I and O the muscles were squeezed about 1 cm rostral to the musculotendinous region. The records were obtained in the decerebrate state (A—D), after a low pontine lesion (E—I) and after spinal transection in L_1. (J—O). The conditioning stimulus strengths, indicated in the records, are expressed in multiples of threshold strength. Each record consists of 5 superimposed traces.

Renshaw inhibition does not extend beyond half a segment (ECCLES, FATT and KOKETSU 1954); hence these combinations could be used. The Ip monosynaptic test reflex was recorded (with a buried electrode) from the nerve to this muscle on stimulation of the 5th lumbar dorsal root. Fig. 12 shows the effect of muscle pressure on the Grac test reflex in the decerebrate state (C and D) after a low pontine lesion (H and I) and in the spinal state (N and O). For comparison the effect of conditioning FDL volleys is shown in the corresponding records to the left. In the decerebrate state neither a strong conditioning volley at 40 times threshold nor firm squeezing of the muscles had any effect. After the pontine lesion the conditioning volleys at 8 times threshold, which is nearly maximal for group II (ECCLES and LUNDBERG 1959 a), had hardly any effect in record F but when the strength was raised to 40 times threshold to include also group III there was a marked inhibition (G) and pressure of the muscles also inhibited the test reflex (I). There was no inhibition when the muscles were stretched. After transection of the cord (Th 12) the same conditioning

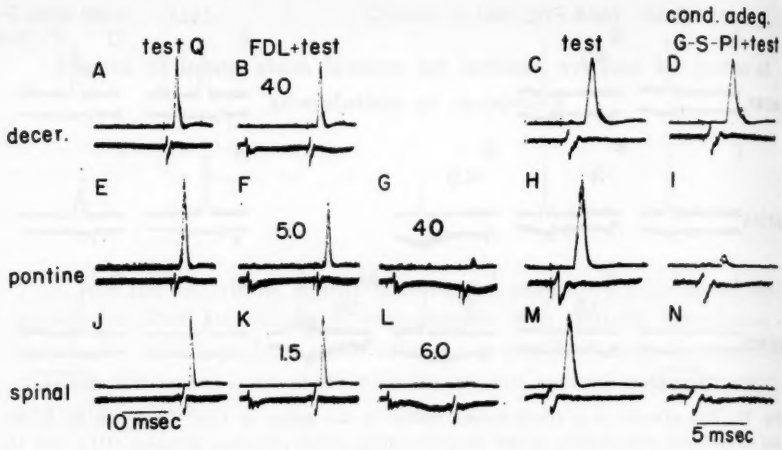

Fig. 13. These records were obtained in the same experiment as those in Fig. 12, but the testing monosynaptic reflex was from the nerve to quadriceps (Q).

volley evoked reflex discharges in the ventral root and facilitated the Grac test reflexes; the increment in facilitation from L to M presumably can be attributed largely to group III fibres. Pressure on the muscle facilitated markedly the test reflex and this effect could be attributed mainly to fibres smaller than group II since strong stretch of the muscle (> 500 g) increased the Grac test reflex by less than 20 per cent.

The corresponding records in Fig. 13 are from the same experiment as Fig. 12 but the monosynaptic test reflex was evoked from the Q nerve. Likewise squeezing of gastrocnemius-soleus-plantaris had no effect in the decerebrate state (D). After the pontine lesion there was profound inhibition (I) and after section of the cord complete inhibition (N).

Bessou and Laporte (1960) have described 3 types of group III muscle afferents: 1) slowly adapting fibres activated by relatively strong compression of the muscle close to the tendon, 2) rapidly adapting fibres activated by localized pressure on the peroneal insertion of soleus, 3) fibres activated by moderate pressure on a limited region of the muscle. We have tested stimuli of these 3 types in a variety of preparations. In the spinal state flexor nuclei are facilitated and extensors inhibited by all these three kinds of stimuli and in addition by a very gentle pressure on the tendon. These effects must have been due largely to fibres smaller than group II because the effects obtained with strong pull of the muscle were much smaller. Compression of the muscle was the most effective stimulus

but very marked effects were also obtained on touch of the muscle belly or of the tendon. In excitable spinal preparation a very gentle pressure (on a surface of approximately 25 mm^2) on the muscle belly or on the tendon was sufficient to evoke a clear cut effect.

In the low pontine preparation test reflexes from G-S were inhibited by all three types of natural stimuli described by BESSOU and LAPORTE and in addition by gentle pressure on the tendon. Inhibition of test reflexes from flexors, on the other hand, was usually found only on compression of the muscle close to the tendon. Only in one experiment did a gentle pressure on the muscle give a slight inhibition. Undoubtedly further experiments are required but our tentative explanation is that the difference in natural stimulation required for evoking excitation and inhibition respectively in flexor motoneurones is quantitative. This difference may be due to a weak linkage to the latter pathway in the low pontine state and cannot at present be taken to indicate that afferents with different receptive functions supply these actions.

B. Skin receptors

HAGBARTH (1952) has shown that the cutaneous effects to flexor as well as to extensor motoneurones are complex. The modality of action depends on the skin area stimulated. Hence for the further analysis of the cutaneous effects in the low pontine preparation it was desirable to use natural stimulation of skin. In these experiments the muscles (except some of the hip) were denervated. The effect of pinching of the skin was examined on the monosynaptic reflex evoked from BSt and in one control experiment also on the test reflexes from DP and Grac. In the spinal preparation the pattern of excitatory and inhibitory skin areas described by HAGBARTH (1952) was usually confirmed but in the decerebrate decerebellectomized animal there was no predictable pattern. In some experiments as in Fig. 14 there was no facilitation of BSt monosynaptic reflexes even on strong pinching of any area of skin of the hindlimb, but a slight inhibition was obtained from the skin (pinching) over the heel (records A and B, Fig. 14). After a low pontine lesion the same stimulation of the skin gave strong inhibition (records C and D) and inhibition was obtained from a wide skin area as is shown in the drawing. After transection of the cord there was facilitation from the skin over the heel (records E and F) as well as from other skin areas, but in accordance with HAGBARTH's scheme inhibition from the skin field overlying quadriceps.

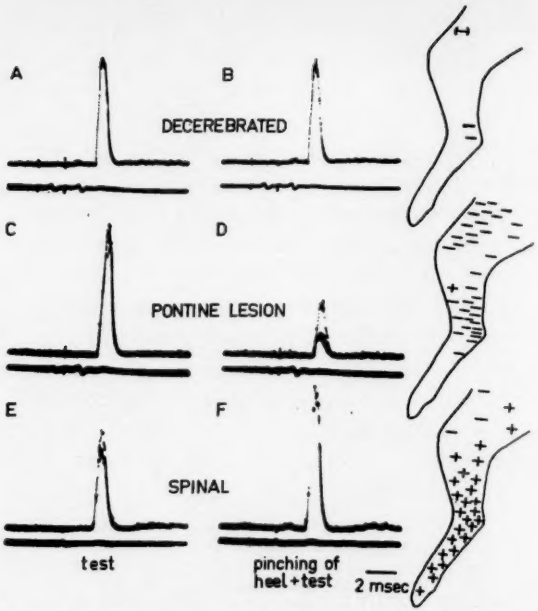

Fig. 14. Effect of natural stimulation of the skin (pinching) on the monosynaptic test reflex from BSt, shown unconditioned in A, C and E (upper traces). Lower traces are triphasic recordings from the dorsal root entry zone. The muscles of the hind limb were denervated except some at the hip; the tibial nerve was cut. Records B, D and F were obtained during pinching of the skin over the heel. The records were obtained in the decerebrate state (A and B), after a low pontine lesion (C and D) and after a spinal transection (E and F). In the corresponding diagrams are shown the receptive skin fields for the excitatory (+) and the inhibitory (—) effects. Brackets denote weak or uncertain effect. Corresponding effects were found on the medial and lateral side of the limb.

Exceptionally there were marked inhibitory effects to BSt in the decerebrated state as is illustrated to the left in Fig. 15 A, with the reversal to facilitation in the spinal state to the right. In other animals the effect from skin in the decerebrate state resembled the one found in the spinal state. This is illustrated in Fig. 15 B where inhibition nevertheless dominated after the low pontine lesion. In Fig. 15 C the test reflex was from DP. It was important to do this control experiment because with test reflexes from BSt it could not be excluded that in the low pontine state a small part of the monosynaptic test discharge was derived from hip extensor motoneurones (*cf.* p. 17). In the experiment of Fig. 15 C no effect was found

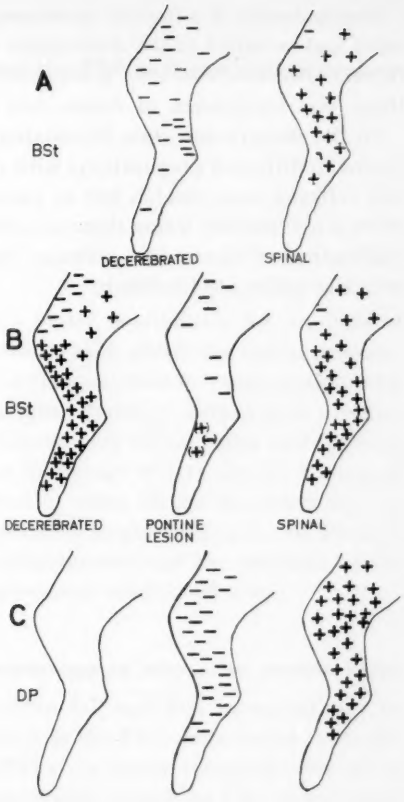

Fig. 15. As in Fig. 14 the diagrams represent the receptive skin fields for excitatory and inhibitory effects evoked by pinching the skin in three experiments A, B, and C. In A and B the monosynaptic test reflex was from the BSt and in C from the DP nerve.

in the decerebrate state on pinching the skin anywhere on the ipsilateral hindlimb but after a low pontine lesion there were strong inhibitory effects from the entire hindlimb on pinching. Also pressure of the skin gave some inhibitory effects in this experiment, whereas in all other experiments pinching was required. In this experiment there was facilitation on light pressure after cord transection; in some of the other experiments marked actions were evoked in the spinal state only when the skin was pinched.

Summary

The effect of natural stimulation of muscle and skin receptors on monosynaptic test reflexes was investigated in the decerebrate preparation, after a low pontine lesion and after spinal transection.

Manipulation of a muscle (pressure) designed to activate group III afferents had no effect in the decerebrate state but inhibited test reflexes from flexors and extensors after a low pontine lesion. After a spinal transection there was facilitation of flexor and inhibition of extensor test reflexes.

In the decerebrate state stimulation of the skin (pinching or pressure) varied in different preparations with respect to the effect on monosynaptic test reflexes from flexors but in some cases there was no or little effect. After a low pontine lesion there was inhibition, and after spinal transection facilitation of flexor test reflexes from a major part of the skin areas over the ipsilateral hindlimb.

Chapter III

Analysis of the inhibitory path from the FRA to flexor motoneurones

The low pontine preparation offers better possibilities for analysis of the inhibitory path to flexor motoneurones than either the spinal preparation (ECCLES and LUNDBERG 1959 a) or the anaesthetized preparation with intact brain (*cf.* Chapter IV). In the latter types of preparation absence of excitatory actions from the FRA is found only occasionally and for each motoneurone it must be excluded that inhibitory effects are not RENSHAW effects secondary to discharges evoked in other flexor motoneurones by volleys in the FRA. In the low pontine state single volleys in the FRA do not excite either flexor or extensor motoneurones and the inhibitory path can be investigated without the complications mentioned above.

A. Intracellular recording from flexor motoneurones after a low pontine lesion

Intracellular recording was made from DP and BSt motoneurones in 5 cats with a low pontine lesion. Volleys in the FRA were found to evoke inhibitory post-synaptic potentials (IPSPs) in flexor motoneurones, as is illustrated in Fig. 16 and 17. The intracellular records in Fig. 16 are from a DP motoneurone and were obtained with a K_2SO_4-electrode. The effect from the Q nerve in C and D, evoked at 3.7 and 7.4 times threshold, can be ascribed to impulses in group II afferents while inhibitory actions from other nerves, FDL (F), BSt (H), Pl and G-S (not illustrated) appeared mainly at group III strengths. Volleys in the sural nerve (I and J) also gave a large IPSP. The joint nerve was not dissected for stimulation in this experiment. In C and D the onset of the IPSP starts 3.2 msec after the incoming group I volley. Considering the conduction velocity of group II fibres this suggests a central latency of 2.8 msec and indicates that the inhibitory path has two interneurones; the same holds true for the path from cutaneous afferents as indicated by the latencies in I and J.

Since the ventral roots were sectioned, antidromic activation from muscle nerves could not be used; motoneurones had to be identified from their pattern of I a convergence (ECCLES *et al.* 1957 b, ECCLES and LUND-

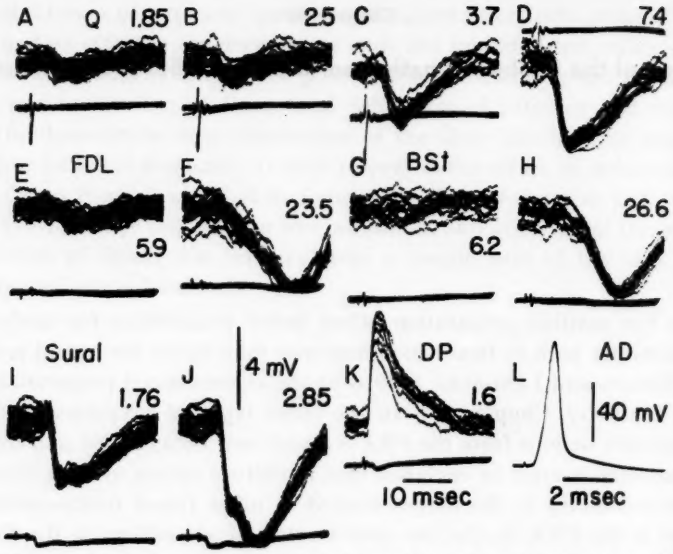

Fig. 16. Intracellular recording (upper traces except in D), with microelectrode filled with 0.6 M K_2SO_4, from a motoneurone of the DP nerve. Lower traces (except in D) are triphasic recordings from the L_6 dorsal root entry zone. The effects were evoked on stimulation of the nerves to quadriceps (Q), (A—D), FDL (E and F), BSt (G and H), DP (K), of the sural nerve (I and J) and of antidromic activation (AD) from the L_7 ventral root (L). The stimulus strengths, expressed in multiples of threshold strength, are indicated in the records. The animal was decerebrated and decerebellectomized and had a low pontine lesion with the approximate location of lesion 3 in Fig. 1. The records consist of many superimposed traces.

BERG 1958). Cells with monosynaptic Ia EPSP from BSt were only accepted as BSt motoneurones if they did not receive monosynaptic Ia excitation from the hip extensors, anterior biceps and semitendinosus (*cf.* ECCLES and LUNDBERG 1958). In Fig. 17 recording (KCl-electrode) was made from a BSt cell after a low pontine lesion. The effects were evoked by volleys in the Q nerve (A—H) and in the G-S nerve (I—P). In order to keep the IPSPs in the hyperpolarizing direction a depolarizing current was passed in A—D and I—L. The reversed IPSPs obtained during passage of a weak hyperpolarizing current are seen in E—H and M—P. The reciprocal Ia IPSP is seen in A and E but the later effects in B—D and F—H were evoked by volleys in high threshold muscle afferents. As in Fig. 16 the effects from high threshold afferents in the Q nerve appeared at lower stimulus strengths and after a shorter latency than the effects

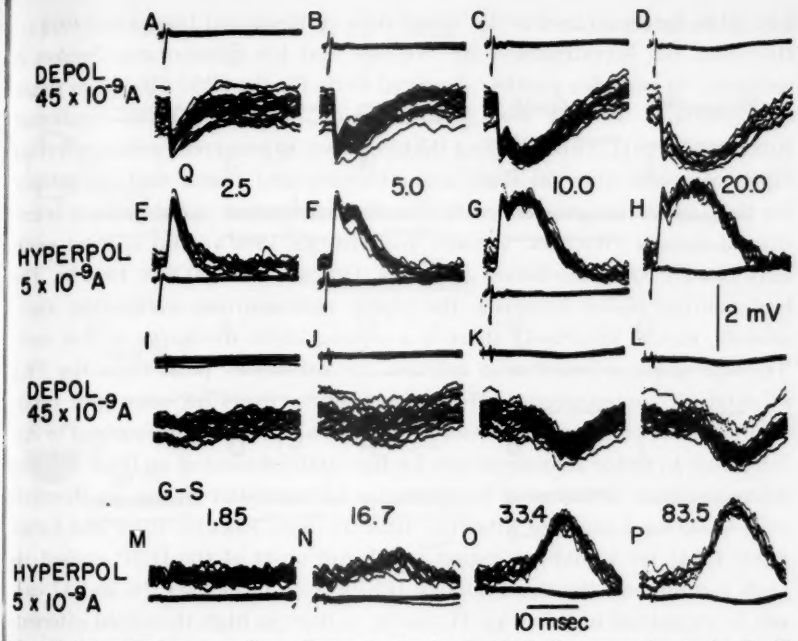

Fig. 17. Intracellular recordings (lower traces in A—D, I—L; upper traces in E—H and M—P) with micro-electrode filled with 3 M KCl, from a motoneurone of the BSt nerve. A—H responses evoked by stimulation of the nerve to quadriceps Q and I—P of the nerve to gastrocnemius-soleus (G-S). A—D and I—L were obtained during passage of a depolarizing current through the recording electrode and E—H and M—P during passage of a hyperpolarizing current. The triphasic records of the incoming volley were recorded from the L_6 dorsal root entry zone in A—H and M—P but from L_7 dorsal root entry zone in I—L. The records consist of many superimposed traces.

from the other nerves. There was no sign of a concealed EPSP. Effects by volleys in homonymous high threshold afferents could not be analyzed in the cells of Fig. 17 since the cell was discharged by the I a volley from the BSt nerve but in other cells it was established that IPSPs were evoked from these afferents as well (*cf.* Fig. 21 and also Fig. 8, ECCLES and LUNDBERG 1959 a).

B. Exclusion of Wilson's disinhibition

When we discovered that after a low pontine lesion volleys in the FRA inhibited flexor test reflexes we took it for granted (HOLMQVIST and LUNDBERG 1959 b) that this was due to a release of the inhibitory path-

way, already recognized in the spinal state (ECCLES and LUNDBERG 1959 a). However, the investigations by WILSON and his collaborators makes it necessary to consider another neuronal route for the IPSPs found in flexor motoneurones after a low pontine lesion. WILSON (1959) confirmed RENSHAW's (1941, 1946) finding that impulses in recurrent collaterals from alpha afferents may facilitate motoneurones and found that the latency for this facilitation may be brief. The effect was most common from extensors to flexors (WILSON, TALBOT and DIECKE 1960 a) and is most probably caused by disinhibition (WILSON, DIECKE and TALBOT 1960 b). The low pontine lesion increases the alpha motoneurone excitability enormously, almost invariably there is a resting alpha discharge in this state. The low pontine lesion also releases the inhibitory path from the FRA to extensor motoneurones. Hence a volley in the FRA may give cessation of alpha activity in extensor motoneurones, leading to removal of disinhibition to flexor motoneurones, *i.e.* the establishment of an IPSP in flexor motoneurones. Because of the prolonged transmitter action in Renshaw cells (ECCLES, FATT and KOKETSU 1954, ECCLES, ECCLES, IGGO and LUNDBERG 1961) we would not expect an abrupt onset of the IPSP evoked via such a route and the short latency IPSPs from Q in Figs. 16 and 17 cannot be explained in this way. However, volleys in high threshold afferents from Q sometimes evoke IPSPs in flexor motoneurones also in the decerebrate state (Fig. 4, ECCLES and LUNDBERG 1959 b, HOLMQVIST and LUNDBERG 1959 a).

That there is a true release of the inhibitory path from the FRA to flexor motoneurones has been proved as illustrated in Fig. 18. Monosynaptic reflexes were recorded from the nerves to medial vastus (med.V) (A—C, K—M, U—W), and Grac (F—H, P—R, Z—BB) (stimulation of the cut 6th lumbar dorsal root). In the decerebrate state supramaximal volleys in the G-S nerve had no action on these test reflexes (not illustrated). After a low pontine lesion there was inhibition of both the extensor and flexor test reflex (B, C and G, H respectively). Recording at higher gain revealed resting activity (presumably in alpha afferents) in the nerve to med.V, D, but not in the nerve to Grac, I. A conditioning volley in high threshold afferents from G-S inhibited this resting activity, E, but had no effect in record J. Thereafter the ventral quadrants were sectioned in L 1. There was a marked decrease in the sizes of monosynaptic reflexes (*cf.* Fig. 7); the dorsal root stimulus was raised in order to evoke a med.V test reflex, and to evoke a Grac test reflex the dorsal root stimulus had to be supported by a double volley from the semitendinosus nerve (*cf.* ECCLES, ECCLES and LUNDBERG 1957 b). *At the same time the resting*

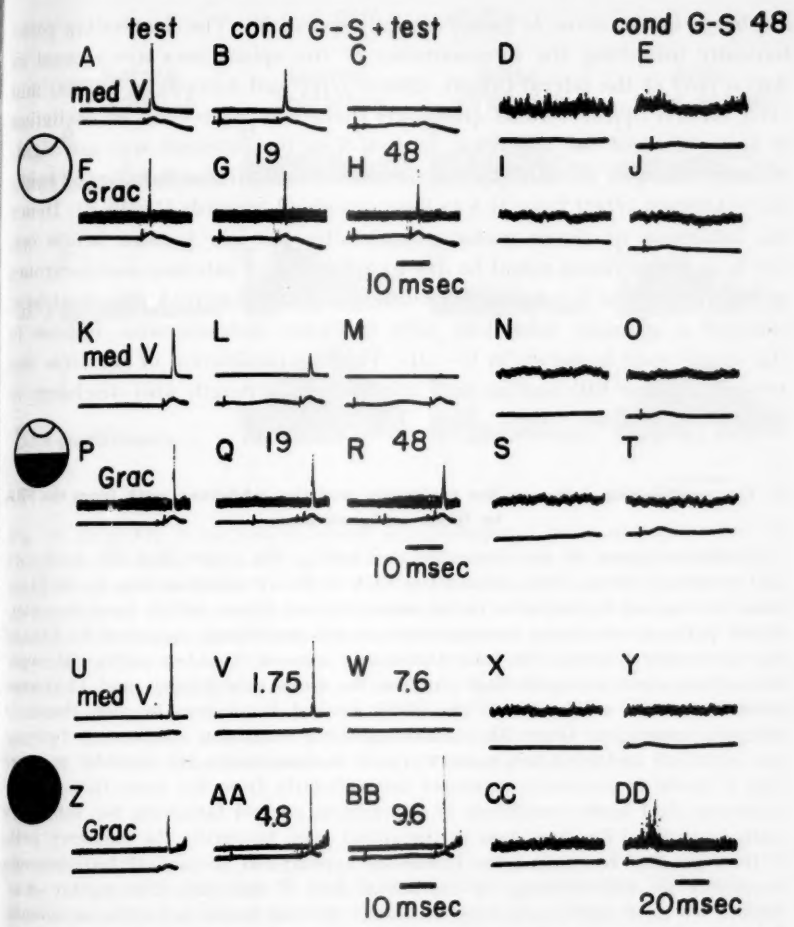

Fig. 18. In the left column is shown the unconditioned monosynaptic test reflexes recorded in the nerves to medial vastus (med. V) (A, K and U) evoked on stimulation of the L_6 dorsal root and to gracilis (Grac) (F, P and Z) evoked on stimulation of the L_6 dorsal root and the semitendinosus nerve. The effects on these test reflexes of conditioning volleys in the nerve to gastrocnemius-soleus (G-S) evoked at the indicated strengths expressed in multiples of threshold strengths, are shown in the corresponding records in the second and the third column. The traces in the fourth and fifth columns were obtained at higher gain from the nerves to medial vastus (D, E, N, O, X, Y) and gracilis (I, J, S, T, CC, DD); in the fourth column without and in the fifth column with stimulation of the gastrocnemius-soleus nerve. The experiment was made on decerebrate cerebellectomized animal with a low pontine lesion with the approximate location of lesion 3 in Fig. 1. As indicated by the symbols to the the left these records were obtained with the spinal cord intact (A—J), after section of the ventral quadrants in L_1 (K—T) and after complete transection of the cord in L_1 (U—DD). The records of the three left columns consist of about 10 superimposed traces. Single traces are shown in the two right columns.

discharge in the nerve to med.V ceased (record N). The descending paths tonically inhibiting the interneurones of the spinal arcs are located in dorsal part of the lateral funicle (HOLMQVIST and LUNDBERG 1959 a) and after section of the ventral quadrants there was no release of excitation to Grac (T) and the inhibition from G-S to the extensor was not significantly changed (L and M). Furthermore, and this is the crucial point, *the inhibitory effect from G-S to Grac remained* (records Q and R). Hence the inhibition of flexor motoneurones after the low pontine lesion can not to any significant extent be due to inhibition of extensor motoneurones giving removal of WILSON's disinhibition and the pontine lesion must have released a 'genuine' inhibitory path to flexor motoneurones. Release to the spinal state is shown in U—DD. There is facilitation of the Grac test reflex (AA and BB) and at high conditioning strength also discharge in Grac motoneurones (DD).

C. The relationship between the excitatory and the inhibitory path from the FRA to flexor motoneurones

It will be shown in the discussion concluding this paper that the inhibitory and excitatory action evoked from the FRA in flexor motoneurones in all likelihood are evoked by impulses in the same afferent fibres, which have two alternative pathways to flexor motoneurones as was tentatively suggested by ECCLES and LUNDBERG (1959 a). The interrelationship between these two paths with opposite action offers an interesting problem. In spinal cats ECCLES and LUNDBERG failed to obtain evidence that the EPSP evoked by volleys in high threshold afferents conceal an IPSP. This could indicate a reciprocal relationship between the excitatory and inhibitory paths to flexor motoneurones, but in order to prove this it would be necessary to record intracellularly from the same flexor motoneurones, first under conditions of supraspinal control favouring the inhibitory path from the FRA, and then in the spinal state favouring the exitatory path.

It is possible to remove the inhibitory supraspinal control of interneurones reversibly by cold blockage of the dorsal half of the cord (HOLMQVIST *et al.* 1960). We have tried extensively to utilize the cold block technique on animals with low pontine lesions in conjunction with intracellular recording, but these experiments failed, presumably due to fragility of the pontine preparation; there was circulatory shock and collapse of the supraspinal control from the brain stem. The cold block technique is exemplified in Fig. 19. The experiment was done on a decerebrate cat. About 15 mm of the ventral quadrants were removed in the lower thoracic region and a thermode inserted under the dorsal cord. In our previous experiments (HOLMQVIST *et al.* 1960) the dorsal column was removed at the site of the block, but now we leave the dorsal column intact thereby improving circulation in the cord over the thermode with the assurance of better reversibility. With a thermode temperature of 0°C it was not possible to block all dorsal column fibres, but by functional tests the blockage of the more ventrally located descending pathways responsible for the supraspinal control of reflex arcs was complete. This is illustrated in Fig. 19 where the upper records

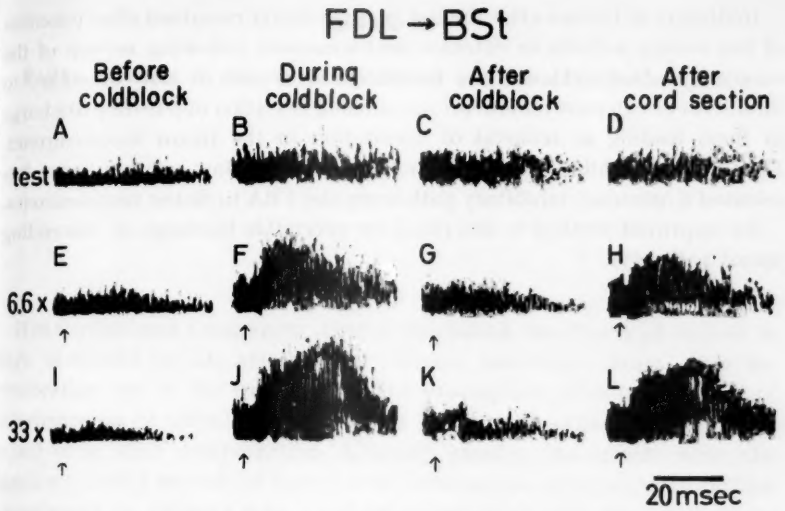

Fig. 19. As in Fig. 7 the records consist of superimposed traces of many reflex discharges evoked from the nerve to BSt. In A—D are shown the unconditioned monosynaptic reflexes, in E—L the effect of a conditioning volley in the nerve to FDL. Arrows indicate the time of arrival at the dorsal root entry zone of the group I volley from the FDL nerve. Conditioning stimulus strengths are given as multiples of threshold strength for the nerve. Records A, E and I were obtained in a decerebrate cat, with the ventral quadrants removed bilaterally in Th_{10}—Th_{12} so a thermode could be inserted under the remaining dorsal parts of the cord. B, F and J were obtained during and C, G and K after cold block of the dorsal cord (thermode temperature 0°C), and D, H and L after transection in Th_{10} of the remaining parts of the cord.

show the unconditioned test reflex from BSt. During the coldblock there is the same release of facilitation (F and J) evoked by a conditioning FDL volley as after transection of the remaining dorsal parts of the spinal cord (H and L). Though the coldblock in B, F and J lasted for 45 min. the recovery was complete in less than 5 min.; the action of the FDL volley is equally well suppressed after the coldblock (C, G and K) as it was before (A, E and J).

Summary

Intracellular recording was made from motoneurones in decerebrate unanaesthetized cats with a low pontine lesion. Volleys in the FRA evoked large IPSPs in flexor motoneurones and there was no evidence of concealed EPSPs. Latency measurements suggest that the shortest inhibitory path to flexor motoneurones has two interneurones.

Inhibition of flexors after the low pontine lesion remained after cessation of the resting activity in extensor motoneurones following section of the ventral quadrants. Hence the inhibition of flexors is not secondary to inhibition of extensor motoneurones causing cessation of a resting discharge in them leading to removal of facilitation in the flexor motoneurones. (WILSON's disinhibition). It is concluded that the low pontine lesion has released a 'genuine' inhibitory path from the FRA to flexor motoneurones.

An improved method is described for reversible blockage of descending spinal pathways.

Chapter IV

Reflex actions in the anaesthetized animal with intact brain

HOLMQVIST and LUNDBERG (1959 a) compared the effects of volleys in high threshold muscle afferents on animals with intact brain, after decerebration and in the spinal state. The supraspinal inhibitory control of interneurones of spinal reflex arcs was less intense, when the brain was intact than after decerebration. Although smaller, the effects when the brain was intact resembled those found after section of the cord. In further experiments on animals with intact brain lightly anaesthetized with Nembutal we have now found that volleys in the FRA in some animals can give considerable inhibition of flexors as is illustrated in Fig. 20. Record A shows the unconditioned monosynaptic BSt test reflex and B—E the effects of conditioning volleys from G-S evoked at 2.1 (maximal for group I), at 5.2, at 10.5 and 21 times threshold. Inhibition of DP was found more frequently than of BSt but in this experiment the DP test reflex was facilitated. Since other flexor nuclei were excited it is difficult to exclude entirely that the inhibition is not a recurrent Renshaw effect (RENSHAW

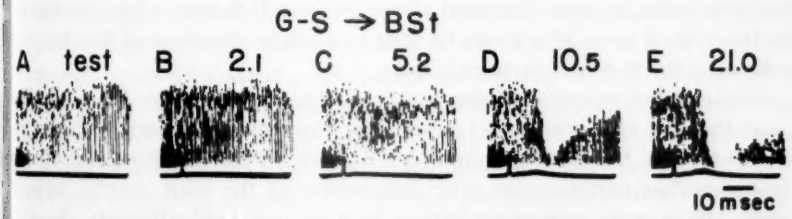

Fig. 20. As in Fig. 7 the records consist of superimposed traces of many monosynaptic reflex discharges but they were evoked from the nerve to BSt and recorded in S_1. The unconditioned test discharges are shown in A and the effect of conditioning volleys from the gastrocnemius-soleus nerve are shown in B—D. Conditioning stimulus strengths relative to threshold strength are indicated in the records. The animal was anaesthetized with Nembutal and the brain was intact. The lower trace is the base line which was not completely suppressed in these recordings. The monosynaptic reflex evoked by the conditioning volley emerges from the baseline and serves as time reference for the incoming volley.

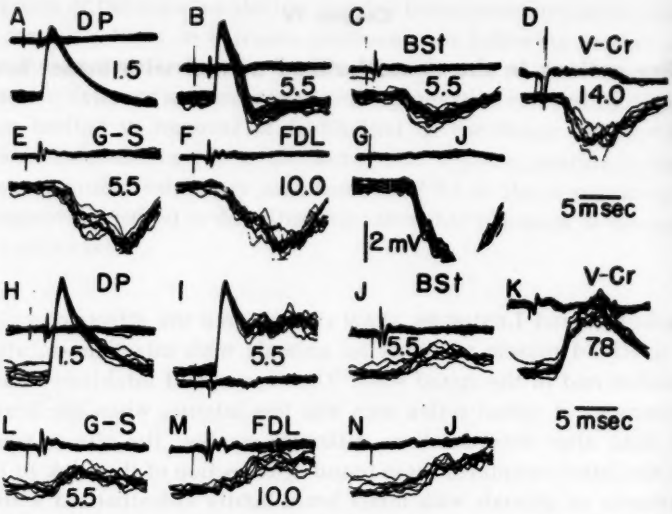

Fig. 21. Lower traces are intracellular recordings with a micro-electrode filled with 0.6 M K_2SO_4 from two DP motoneurones, A—G and H—N respectively. The upper traces in the records were recorded from the dorsal root entry zone. The brain of the animal was intact and A—G were obtained before and H—N after transection of the spinal cord in L_1. The following nerves were stimulated: DP (A, B and H, I), BSt (C and J), vastocrureus (V-Cr) (D and K), gastrocnemius-soleus (G-S) (E and L), FDL (F and M) and the posterior nerve to the knee joint (J) (G and N). The stimulus strengths relative to threshold strength are indicated in the records.

1941, 1946, Eccles *et al.* 1954); the base line in D and E actually reveals that the volley in high threshold afferents from G-S gave a late discharge in the ventral root, which can be seen as a slight elevation of the basline following the G-S monosynaptic spike.

Intracellular recording from motoneurones was also made in lightly anaesthetized cats with intact brain. The intracellular records in Fig. 21 are from two DP motoneurones; A—G were obtained before and H—N from another motoneurone after transection of the cord. In the former state, IPSPs were evoked by volleys in high threshold afferents (B—G), while in the spinal state these volleys gave EPSPs (I—N). It should be noted that volleys from extensors and flexors are equally effective in giving these two sets of actions. In the experiment of Fig. 21 inhibition dominated in all of the 6 DP motoneurones recorded from before transection of the cord. 4 DP motoneurones were found after transection of the cord, and, in all of these, volleys in high threshold afferents evoked EPSPs. BSt motoneurones investigated in the same experiment received

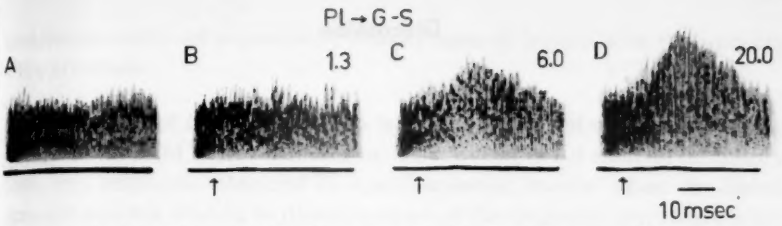

Fig. 22. As in Fig. 7 but conditioning volleys in the plantaris nerve (Pl) and monosynaptic test discharges evoked from the gastrocnemius-soleus nerve. The brain was intact and the cat lightly anaesthetized (Nembutal). Arrows indicate the time of arrival at the dorsal root entry zone of the group I volley from the plantaris nerve. Conditioning stimulus strengths are expressed in multiples of the threshold strength; a maximal group I volley was evoked at 1.3 times threshold.

excitatory action from these afferents also before transection of the cord. The inhibitory effects in the DP motoneurone of Fig. 21 were not a secondary Renshaw inhibition caused by the discharge in other flexor motoneurones, because these IPSPs were evoked at stimulus strengths lower than those required for reflex discharge from the FRA in the ventral root used for recording as well as in the adjacent roots. Stimulation at 10/sec was used to depress reflex excitation.

In the spinal state extensor motoneurones receive predominantly inhibitory actions from the FRA. There is, however, apart from the extensor thrust, considerable evidence of ipsilateral extension reflexes from skin (Graham Brown 1911, 1912; Graham Brown and Sherrington 1912, Hagbarth 1952). Eccles and Lundberg (1959 a) found that volleys in high threshold muscle afferents occasionally could evoke EPSPs in extensor motoneurones. The records in Fig. 22 are from an experiment on a lightly anaesthetized animal with intact brain in which volleys in high threshold afferents from Pl caused considerable facilitation of G-S monosynaptic test reflexes. There was also a corresponding facilitation of G-S from the nerves to anterior biceps and BSt. On the other hand in the same experiment test reflexes from Q were inhibited by volleys in high threshold afferents from G-S, Pl and FDL. Even if the findings in this experiment are exceptional they may, like the intracellular finding, be indicative of an excitatory path to extensor motoneurones from high threshold muscle afferents.

Summary

In lightly anaesthetized animals with intact brain volleys in the FRA may evoke large inhibitory actions in flexor motoneurones. In one case facilitation of extensor motoneurones was evoked by volleys in high threshold muscle afferents.

Discussion

This investigation has been concerned with the supraspinal control of spinal reflex arcs activated by I b afferents and of those activated by the flexion reflex afferents (FRA) but the discussion will be confined to the control of the latter pathways.

The supraspinal inhibitory control of the interneurones of the flexion reflex arcs was originally revealed by a comparison of the effect by single volleys in the FRA in decerebrate and spinal cats (JOB 1953, ECCLES and LUNDBERG 1959 b). The present experiments with natural stimulation of muscle and skin in the decerebrate and spinal states supplement these findings and illustrate well the effectiveness of this inhibitory control.

New aspects on the organization of the inhibitory supraspinal control or the spinal reflex actions by the FRA have been gained through the experiments in which the release from this control was investigated after lesions at various brain stem levels. *After a low pontine lesion there is release of the inhibitory pathway to extensor motoneurones, whereas release of the excitatory path to flexor motoneurones occurs only after a more caudal medullary lesion* (Fig. 1—4). Since the low pontine lesion gives an almost complete release of the inhibitory path to extensor motoneurones without any release of the excitatory path to flexor motoneurones it is unlikely that the effect is due merely to a quantitative difference. A more reasonable explanation is a rostral location of the cells giving rise to the descending tract inhibiting the inhibitory path to extensor motoneurones in relation to the cells giving rise to the tract inhibiting the excitatory path to flexor motoneurones. It is, however, possible that the release is due to interference with centres controlling the activity of these descending tracts rather than with the neurones of these descending tracts. In any case the differential effect of the lesions strongly suggests that separate descending neuronal systems are responsible for the inhibitory control of the reciprocal paths from the FRA to extensor and flexor motoneurones. Hence there is also the possibility of a differential functional control of these reflex paths and that reciprocal innervation of flexor and

motoneurones is not a necessary consequence of impulses in the primary FRA afferents.

A major part of this investigation has been concerned with an *inhibitory path from the FRA to flexor motoneurones*. Evidence for such an inhibitory path was originally obtained in spinal animals mainly when the blood pressure was low leading to disappearance of the normally prevalent excitatory actions from the FRA (ECCLES and LUNDBERG 1959 a). These inhibitory actions were more common in DP motoneurones but were observed also in other flexor motoneurones. In unanaesthetized high spinal animals PAINTAL (1961) also frequently found inhibition of DP (but not of BSt) monosynaptic reflexes by group III volleys from gastrocnemius-soleus. In addition we have now found marked inhibitory actions to flexor motoneurones in anaesthetized animals with intact brain (Fig. 20 and 21) though usually the excitatory effects dominate (*cf.* HOLMQVIST and LUNDBERG 1959 a). In the decerebrate state both the inhibitory and the excitatory path is usually closed (*cf.* however ECCLES and LUNDBERG 1959 b, HOLMQVIST and LUNDBERG 1959 a) *but a low pontine lesion releases the inhibitory path from the FRA to flexor motoneurones without release of the excitatory path.* This inhibition reached all flexor nuclei investigated (iliopsoas, gracilis, posterior biceps, semitendinosus, tibialis anterior and extensor digitorum longus).

Intracellular recordings revealed that in the low pontine state volleys in the FRA evoke IPSPs in flexor motoneurones, but, even so, it could not without further analysis be concluded that the low pontine lesion had released the inhibitory path found in the spinal preparation (ECCLES and LUNDBERG 1959 a). The low pontine lesion also gives a very marked increase of alpha excitability (Fig. 7) with resting discharge in alpha motoneurones. Furthermore this lesion also releases the inhibitory paths from the FRA (*cf.* above) to extensor motoneurones, thus volleys in FRA can decrease the resting activity in extensor motoneurones. This might lead to removal of recurrent facilitation in flexor motoneurones (WILSON 1959, WILSON *et al.* 1960 a), and, since recurrent facilitation is caused by disinhibition (WILSON *et al.* 1960 b), to the establishment of IPSPs in flexor motoneurones (*cf.* p. 31). It was, however, possible to exclude that after a low pontine lesion any major part of the inhibition evoked from the FRA in flexor motoneurones had this origin, because the inhibition remained after the spontaneous activity in the motoneurones had ceased following a ventral section of the spinal cord with interruption of pathways tonically exciting motoneurones (Fig. 18). It is therefore concluded that the low pontine lesion has released a 'genuine' inhibitory path from the FRA to flexor motoneurones.

The low pontine lesion also releases inhibitory paths from the FRA to contralateral flexor and extensor motoneurones whereas crossed excitation is released only by a more caudal lesion (HOLMQVIST 1960, 1961). It is extremely interesting that the centres controlling the excitatory and the inhibitory paths from the FRA to motoneurones presumably are located at different levels in the brain stem. This finding may very well be a clue to principles according to which these supraspinal centres establish their descending connexions. It should, however, be noted that this generalization only holds with respect to the control of the effects evoked by the FRA; the I b inhibitory path is not released by the low pontine lesion but only by a more caudal lesion. For the time being we have not tried to study the location and organization of those centres in the reticular formation, but have been concerned with the consequences of our findings for the understanding of the organization at the segmental level of the spinal cord.

The finding that volleys in the FRA can inhibit as well as excite flexor nuclei raises the question whether there may be *two types of flexor motoneurones, one group receiving excitation and the other inhibition from the FRA.* The fact that the monosynaptic reflexes from flexors may be completely inhibited by volleys in the FRA is against this explanation and experiments with intracellular recording do not support this possibility. In spinal cats inhibitory effects by these afferents are not uncommon in flexor motoneurones, but in some animals in good condition in which extensive sampling from various flexor nuclei was made, excitatory action was found in all flexor motoneurones (ECCLES and LUNDBERG 1959 a). Furthermore it has also been demonstrated in many motoneurones of spinal cats that convergence of excitatory and inhibitory actions from the FRA to flexor motoneurones may occur (ECCLES and LUNDBERG 1959 a) and actually is rather common (HOLMQVIST and LUNDBERG, unpublished).

To account for the excitatory and the inhibitory pathway to flexor motoneurones from the FRA two alternatives remain:

1) *The excitatory and the inhibitory paths may be supplied by the same afferents.*
2) *The excitatory and the inhibitory paths to flexor motoneurones may be supplied by afferents of different receptive function.*

Of these two alternatives we are for circumstantial reasons decidely in favour of the former. Our main reason for this view stems from the similarity in the receptive fields from which the inhibitory and excitatory actions to flexor motoneurones are drawn. Either effect can be evoked from all the systems comprising the FRA; skin afferents, high threshold

joint afferents and high threshold muscle afferents. In particular it should be noted that for both actions there is the same peculiar convergence from extensors and flexors. With the second of the two alternatives discussed we would have to assume two sets of receptor systems from skin, muscle and joint with afferents in the same diameter ranges, and both of them supplying actions to flexor motoneurones from the same extensive fields. Hence it seems much more reasonable to postulate that the same afferent fibres have two pathways to flexor motoneurones and though the evidence is entirely circumstantial in nature, it is in our opinion strong enough virtually to exclude the second alternative.

This postulate has been developed from our concept that actions by the FRA should be recognized as a pattern with functional unity. This concept is based not only on the fact that these afferent systems all evoke similar effects in motoneurones but also on the finding that actions from these systems converge to the neurones of no less than 4 ascending spinal pathways. (LAPORTE, LUNDBERG and OSCARSSON 1956 b, HOLMQVIST, LUNDBERG and OSCARSSON 1956, OSCARSSON 1957, 1958, LUNDBERG and OSCARSSON 1960, 1961.) As for the motoneurones the receptive fields of the neurones belonging to these pathways are very large with convergence from high threshold muscle afferents of extensors and flexors. Transmission to these ascending pathways is controlled from supraspinal centres in a very similar way as the flexion reflex actions (ECCLES and LUNDBERG 1959 b, HOLMQVIST and LUNDBERG 1959 a, HOLMQVIST *et al.* 1960). It is not known to which extent convergence from the FRA to the motoneurones and to these ascending pathways occurs at an interneuronal level, but extensive convergence from high threshold muscle afferents and cutaneous afferents is found to many interneurones in the dorsal horn (ECCLES, FATT and LANDGREN 1956, KOLMODIN 1957, HUNT and KUNO 1959, ECCLES, ECCLES and LUNDBERG 1960).

The advantage with the term FRA is obvious, but it should be noted that actions evoked by cutaneous afferents and by high threshold muscle and joint afferents can only be ascribed to the FRA, if they are evoked by all these afferent systems. It is possible that each of these receptor systems in addition have other specialized central pathways.

In a preliminary report of this work attention was drawn to the effects by volleys in low threshold group II fibres after various lesions in the brain stem. (HOLMQVIST and LUNDBERG 1959 b). Group II fibres from gastrocnemius-soleus have quantitatively been identified as spindle afferents with flower spray endings (HUNT 1954). Among the FRA low threshold group II volleys from this muscle, which in the spinal state evoke excitatory action in flexor nuclei, can give pronounced inhibitory action after a low pontine lesion (Fig. 5). Since there is no reason to assume two subgroups of spindle afferents with flower spray endings it was inferred that the same fibres have one excitatory and one inhibitory path to flexor motoneurones. Recently PAINTAL (1960) has questioned the receptive homogenity of group II muscle afferents. He claims that in the group II range there is a

significant number of pressure-pain afferents of the kind, which dominate the group III range. PAINTAL has not given a quantitative evaluation of the 'contamination' of group II and it is therefore difficult to appreciate the significance of his claim. These pressure-pain afferents were, however, found mainly in the high threshold group II range and presumably the above argument will retain its validity for low threshold group II actions.

It is also important to consider inhibitory and excitatory effects in flexor motoneurones by natural stimuli known to activate the FRA. PAINTAL's (1961) experiments with natural stimulation of muscles are of interest in this context. He found that pressure on the lateral gastrocnemius-soleus muscle inhibited or facilitated DP monosynaptic reflexes in accordance with the modality of effect evoked by single volleys in group III afferents from the lateral gastrocnemius-soleus nerve. The present comparison of the effect of natural stimulation of muscle or skin in the decerebrate, pontine and spinal states gives a powerful illustration of the flexibility imposed by the supraspinal control of spinal reflex arcs. Natural stimulation of muscle, chosen for activation of high threshold afferents (PAINTAL 1960, BESSOU and LAPORTE 1960, 1961) inhibits flexor nuclei in the low pontine preparation (Fig. 12) and likewise on adequate stimulation of skin inhibition is provided from a field which may comprise the entire hindlimb (Fig. 15). After transection of the cord the same kind of stimuli gives facilitation from muscle and skin with the exception of the expected inhibition from the skin over the antagonist muscle (*cf.* HAGBARTH 1952). Natural activation of joints have not been employed since the receptor function of the numerous joint afferents in the range (7—2 μ) which belong to the FRA is unknown. *In summary,* natural stimuli, known to activate the FRA have been tested with respect to their ability to inhibit or facilitate flexor motoneurones, but so far there is no evidence that the inhibitory and excitatory paths require different natural stimuli. Further experimentation along this line with more differentiated stimuli will certainly be needed when we acquire more detailed informations about receptors connected with the FRA.

Further investigations are needed to disclose the functional *relationship between the excitatory and the inhibitory paths from the FRA to flexor motoneurones.* Although inhibitory action from high threshold muscle afferents to flexor motoneurones are rather common in the spinal cat and convergence of excitatory and inhibitory action is found frequently (*cf.* above), it should be noted that in a number of flexor motoneurones with large EPSPs from high threshold muscle afferents there was no evidence

of concealed IPSPs (ECCLES and LUNDBERG 1959 a). This may indicate a reciprocal linkage between the excitatory and inhibitory paths to flexor motoneurones, which would be functionally meaningful, but in order to decide this question finally, the synaptic actions should be analysed in the same motoneurones, first under conditions of supraspinal control giving optimal opening of the inhibitory path and then in the spinal state. The technique of reversible blockage of the descending controlling pathways (HOLMQVIST *et al.* 1960) was tried for this purpose (Fig. 19) but, so far, our attempts to perform the experiment have failed.

It is also possible that there are alternative pathways from the FRA to ipsilateral *extensor motor nuclei*. There are several reports on ipsilateral extensor reflexes from skin (SHERRINGTON and SOWTON 1911, GRAHAM BROWN 1911, 1912, GRAHAM BROWN and SHERRINGTON 1912, HAGBARTH 1952), but before ascribing these reflexes evoked on stimulation of cutaneous nerves to the FRA, it should be excluded that they represent more specialized reflexes. KUGELBERG, EKLUND and GRIMBY (1960) have recently studied nociceptive spinal reflexes in man and found a harmonious integration of flexion and extension reflexes designed to defend the limb with maintenance of posture. The inhibitory path from the FRA to extensor motor nuclei is very dominant in spinal cats but intracellular recordings have sometimes revealed excitatory action evoked by volleys in high threshold muscle afferents (ECCLES and LUNDBERG 1959 a), and one example of substantial facilitation of an extensor nucleus by volleys in high threshold muscle afferents was reported above (Fig. 22). It is difficult to assess these findings at present but it may be worth while to look for excitatory actions from the FRA to extensor motoneurones under different conditions of supraspinal control. In this connexion it is of great interest that volleys in the FRA on the contralateral side can evoke either excitatory or inhibitory action in both flexor and extensor motoneurones (HOLMQVIST 1960, 1961).

Our results give new aspects on the functional significance of the reflex actions from the FRA. Following the disclosure of the strong inhibitory supraspinal control of the interneurones mediating the actions from FRA it was suggested that these reciprocal actions more or less could be switched off so as to permit optimal regulation of movement by the I a and I b systems (ECCLES and LUNDBERG 1959 b, LUNDBERG 1959). For this suggestion, which still remains a reasonable possibility, it was an inherent assumption that the reciprocal reflex actions to flexors and extensors as expressed by SHERRINGTON (1906) were: 'part and parcel of one

and the same reflex reaction'. A reciprocal organization of reflex actions has been found under a variety of circumstances (SHERRINGTON 1906, 1910) but our findings show that it is not a requisite result of a given volley in the FRA. It seems likely that supraspinal centres may exert a differential control of the reciprocal actions from the FRA to extensor and flexor motoneurones and hence that they are not necessarily a physiological unity when governed by higher centres. Furthermore there is the possibility that higher centres may choose between an excitatory and inhibitory channel to flexor motoneurones. Meanwhile it should also be remembered that there is another supraspinal control system governing the transmittability of pathways from the FRA to motoneurones. Activity in the pyramidal tract facilitates interneurones mediating the flexion reflex actions as well as interneurones of the I b pathways and of the I a inhibitory pathway (LUNDBERG and VOORHOEVE 1961 a).

General Summary

1. The synaptic actions evoked through spinal reflex paths in motoneurones by impulses in somatic afferents have been investigated under different conditions of supraspinal control. The technique of conditioning monosynaptic reflexes has been used as well as intracellular recording from motoneurones. Effects of single volleys and of natural stimulation of muscle and skin have been investigated.

2. In the decerebrate state the reflex actions by volleys in the FRA (flexion reflex afferents: group II and III muscle afferents, high threshold joint and cutaneous afferents) are suppressed due to a tonic inhibitory control from the brain stem of the interneurones of these reflex arcs (ECCLES and LUNDBERG). The release from this supraspinal control has been investigated after lesions at different brain stem levels.

3. After a low pontine lesion there is release of the inhibitory path from the FRA to extensor motoneurones and, in addition, release of an inhibitory path from these afferents to flexor motoneurones. The low pontine lesion increases the alpha excitability very markedly and this fact has to some extent complicated the analysis.

4. Release of the excitatory path to flexor motoneurones occurs only after a more caudal lesion in the medulla.

5. It is inferred that the pathways conveying the reciprocal actions of excitation to flexor and inhibition to extensor motoneurones from the FRA are controlled from the brain stem by separate neuronal systems and suggested that these reciprocal actions can be differentially controlled from supraspinal centres.

6. It is further postulated that the excitatory and inhibitory actions from the FRA to flexor motoneurones are evoked by impulses in the same afferent fibres and that supraspinal centres can select either path for function.

Acknowledgement. This investigation was supported by grants from the Swedish Medical Research Council. We are indebted to Mr E. Eide for construction of electronic equipment. Technical assistance was given by Miss Karin Ebbesson.

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